Treatment of Hepatitis C in Liver Transplant Patients: Interferon OUT, Direct Antiviral Combos IN

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Abbreviations:
hepatitis C virus (HCV)
hepatocellular carcinoma (HCC)
liver transplantation (LT)
direct-acting antivirals (DAAs)
protease inhibitors (PIs)
Food and Drug Administration (FDA)
peginterferon (PEG-IFN)
ribavirin (RBV)
sustained virologic response (SVR)
extended rapid virologic response (eRVR)
erythropoietin (EPO)
dose-normalized (DN)
area under the curve (AUC)
post-transplant virologic response (pTVR)
low accelerating dose regimen (LADR)
Compassionate Use of Protease Inhibitors in Viral C Cirrhosis (CUPIC)
hepatic venous pressure gradient (HVPG)
sofosbuvir (SOF)
end of treatment (EOT)
lower limit of quantification (LLOQ)
simeprevir (SIM)
ledipasvir (LDV)
daclatasvir (DCV)
asunaprevir (ASV)

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ABSTRACT

Although chronic infection with hepatitis C virus (HCV) is the leading indication for liver transplantation in the United States, graft and patient survival rates are reduced due to HCV recurrence after transplant. Interferon-based antiviral treatment administered either prior to or after transplant to prevent or treat HCV recurrence, respectively, is limited due to poor tolerability and low efficacy. However, the treatment of HCV in the transplant setting is changing considerably with the availability of newer direct-acting antivirals and interferon-free regimens. This article will review the experience to date treating HCV in the setting of cirrhosis and LT and will discuss the unique challenges encountered when treating this population.

Chronic infection with hepatitis C virus (HCV) affects an estimated 170 million individuals worldwide and is a leading cause of end stage liver disease and hepatocellular carcinoma (HCC)(1). HCV is the most common indication for liver transplantation (LT) in the United States(2). Due to HCV recurrence in the transplanted liver, overall risk of graft loss is approximately 30% lower in HCV-infected LT recipients compared to HCV-uninfected LT recipients(3). The clinical course of chronic HCV is accelerated post-LT, and 32-51% of patients develop ≥F2 fibrosis (on a scale of 4) within five years of LT(4). In addition, 2-9% of patients develop rapidly progressive severe recurrent HCV (cholestatic variant) within the first year of LT(5). Thus, the timeline for intervention to prevent graft loss is limited for many patients. The goals of HCV therapy in the transplant setting are to prevent liver-related complications and graft loss due to recurrent HCV, and natural history studies have established that post-LT outcomes are improved if HCV is successfully eradicated with antiviral therapy(6).

The discovery of potent, well-tolerated oral direct-acting antivirals (DAAs) has led to dramatic and rapidly evolving changes in the treatment of HCV. The first two NS3/4A protease inhibitors (PIs), telaprevir and boceprevir, were approved by the US Food and Drug Administration (FDA) in 2011 for use in combination with peginterferon (PEG-IFN) and ribavirin (RBV) to treat chronic HCV genotype 1 (Table 1). Simeprevir, a second wave PI, was approved for use in combination with PEG-IFN and RBV for genotype 1 disease by the FDA in November 2013, and by the European Commission (EC) for genotypes 1 and 4 in May 2014 and mostly recently, in November 2014 for use in combination with sofosbuvir in genotype 1. In December 2013, the FDA approved the first nucleotide NS5B polymerase inhibitor, sofosbuvir, which has pan-genotypic activity; sofosbuvir was approved by the EC in January 2014 and is also approved for use in Canada, Australia, New Zealand, Egypt, Switzerland, and Turkey. In July 2014, the Japanese Ministry of Health Labor and Welfare approved daclatasvir, a pan-genotypic NS5A replication complex inhibitor, and asunaprevir, a PI, for genotype 1b disease. Daclatasvir was approved by the EC in August 2014. Finally, the fixed-dose combination of ledipasvir, an NS5A inhibitor, and sofosbuvir was approved by the FDA and Health Canada in October 2014 and was approved in New Zealand and by the EC in November 2014. With the availability of these and future DAAs, the era of interferon-based HCV treatment is coming to an end. While this is a welcome development for all patients with chronic

HCV, the combination DAA therapy will have a profound and immediate impact on the success of antiviral treatment in the HCV-infected LT population.

Two treatment strategies are currently employed in the management of HCV in the transplant setting. The first treats wait-listed patients with the aim of achieving viral clearance on treatment in order to prevent recurrent infection of the graft post-LT. The second, and until now more commonly used strategy, treats patients post-LT who have progressive or severe disease with the aim of achieving a sustained virologic response (SVR). Achievement of virologic response, either prior to or after transplant, was difficult to accomplish with dual therapy of PEG-IFN and RBV due to the poor tolerability and low efficacy. Although addition of the first DAAs, telaprevir and boceprevir, improved rates of response, tolerability remained a major barrier. The availability of DAA combinations that eliminate PEG-IFN provide a major improvement in tolerability and applicability of therapy in these settings and elimination of ribavirin can be anticipated to additionally improve tolerability. Furthermore, a third strategy may emerge: treating patients with decompensated cirrhosis with the goal of achieving SVR in the hopes of *avoiding* LT.

PRE-TRANSPLANT ANTIVIRAL THERAPY IN COMPENSATED CIRRHOSIS

Pre-transplant treatment to achieve SVR

Achievement of SVR prior to LT will prevent HCV recurrence post-LT(7, 8). However, this requires a full treatment course, which until recently was a full 48 weeks of PEG-IFN-based treatment. Interferon-free options are currently available for patients with *compensated* cirrhosis, even with genotype 1 disease (Tables 2, 3). With the current DAA regimens, a full treatment course can be a short as 3 months, depending on regimen and genotype, making treatment with SVR intent a more reasonable option for wait-listed patients with compensated cirrhosis, such as patients with HCC.

Although sofosbuvir and weight-based RBV is effective across genotypes, treatment duration and efficacy vary. For genotype 2, SVR is high with 12 weeks of treatment even if cirrhosis is present. However, limited data among

cirrhotic treatment-experienced genotype 2 patients suggest improved SVR with extension to 16 weeks of treatment(9). For genotype 3, the recommended treatment duration of sofosbuvir and RBV is 24 weeks. Although this yields relatively high SVR (approximately 90%) in most patients, SVR is lower among treatment-experienced cirrhotic patients (60%). More effective all-oral DAA regimens are therefore still needed in this population.

At present, patients with genotype 1 have three options for interferon-free treatment. Dual therapy with sofosbuvir and RBV for 24 weeks is FDA approved for genotype 1 patients who are PEG-IFN-ineligible(10). Among treatment-naïve patients, this regimen yields 50-84% SVR rates (overall 72%). However, there are limited data on efficacy among patients with cirrhosis and treatment experience. Response is predicted to be lower than in treatment-naïve patients. Until recently, a favored option for many providers has been the ~~the FDA off-label but AASLD-IDSA endorsed~~ combination of simeprevir and sofosbuvir, with or without RBV, for 12 weeks(11). Twelve and 24 week therapy of simeprevir and sofosbuvir with or without RBV among patients with compensated METAVIR F3-F4 disease yields SVR rates of 93% and 96%, respectively (12). Response rates are high even in patients with cirrhosis and prior null response to interferon-based treatment. Relapse is highest in patients with genotype 1a. However, the safety of simeprevir has not been evaluated in patients with decompensated cirrhosis (Child-Pugh B and C), and therefore its pre-LT use is limited to patients with compensated disease such as those with HCC. Twelve weeks of treatment with the most recently FDA-approved combination of ledipasvir-sofosbuvir yields 97% SVR among treatment-naïve compensated cirrhotics(13). For treatment-experienced patients with compensated cirrhosis treated with ledipasvir-sofosbuvir, SVR is 86% and 100% with 12 and 24 weeks, respectively (13, 14). Therefore, the FDA-approved duration of ledipasvir-sofosbuvir is 12 weeks for treatment-naïve cirrhotics and 24 weeks for treatment-experienced cirrhotics.

Additional DAAs in development appear to have excellent efficacy among patients with compensated cirrhosis (Tables 2,3). The largest trial among cirrhotics examined the efficacy of the combination of ritonavir-boosted paritaprevir/ritonavir (NS3/4A PI), ombitasvir (NS5A inhibitor), dasabuvir (nonnucleoside NS5B polymerase inhibitor), and RBV among 380 HCV genotype 1 patients with compensated cirrhosis, the majority of whom were treatment

experienced(15). SVR12 rates for 12 and 24 week treatment durations were 92% and 96%, respectively, and were highest in the patients with genotype 1b.

Pre-transplant treatment to prevent HCV recurrence

A treatment course aimed at achieving an undetectable HCV RNA on-treatment and at the time of transplant (rather than SVR) can also significantly reduce, although not completely eliminate, the risk of post-LT HCV recurrence (7, 8, 16-20). Duration of pre-LT antiviral therapy is important in predicting post-transplant virologic response (pTVR). In the A2ALL cohort study, 44 patients were randomized to and received a low accelerating dose regimen (LADR) of PEG-IFN and RBV prior to LT(18). At the time of transplant, 59% had undetectable HCV RNA, and 42% of these patients (25% of all patients) had pTVR. Among patients with undetectable HCV RNA at LT who were treated for <8 weeks, 8-16 weeks, or >16 weeks, pTVR was achieved in 0%, 27%, and 78%, respectively (0%, 18%, and 50% overall). While this study did not directly evaluate duration of HCV RNA negativity as a predictor of pTVR, the findings suggest that the duration matters, although the optimal duration of negativity pre-LT that guarantees pTVR is not known and may differ for an interferon-based vs interferon-free regimen. Interferon-based treatment pre-LT carries risk to the patient: compared to untreated controls, wait-listed patients treated with PEG-IFN and RBV are more likely to experience serious adverse events, including infection(18). The addition of telaprevir or boceprevir in combination with PEG-IFN and RBV leads to higher on-treatment virologic response, even among patients with cirrhosis (21). However, the favorable on-treatment response is tempered by high rates of treatment-associated adverse effects, including severe anemia, serious infections, and hepatic decompensation(21, 22). Thus, the collective experience with the first generation PI-based triple therapy has demonstrated that while on-treatment response is improved, the risks among patients with advanced cirrhosis are unacceptably high when safer options are available.

With the availability of the newer DAAs, PEG-IFN has no role in pre-LT antiviral therapy aimed to prevent post-LT HCV recurrence, especially when the goal is to achieve on-treatment virologic response, rather than SVR. In published

reports of daily sofosbuvir with weight-based RBV, on-treatment virologic responses are nearly universal, regardless of genotype(9, 23, 24). For genotype 1 patients, on-treatment virologic response is also high with the combination of simeprevir and sofosbuvir, with or without RBV, and with ledipasvir-sofosbuvir, even among patients with cirrhosis and prior treatment response(12).

Efficacy and safety data for pre-LT dual therapy with sofosbuvir and RBV exist but are limited. A phase 2 pilot study treated 61 patients listed for LT with HCV genotype 1-4 and MELD exception points for HCC with daily sofosbuvir and weight-based RBV(25). This patient population was selected because they had relatively preserved synthetic function with baseline Child-Pugh score was ≤8 in all patients and 73% were Child-Pugh A. The majority were treatment-experienced. Among the 43 who remained on treatment and had HCV RNA less than the lower limit of quantification at the time of transplant (93%), pTVR was achieved in 70% of patients who were undetectable at the time of LT. In this pilot study, duration of treatment was not significantly associated with HCV recurrence, but duration of *continuously* undetectable HCV RNA was: among 26 patients with continuously undetected HCV RNA for at least 30 days, only 1 recurred post-transplant. Treatment in this group was well tolerated, with a similar safety profile as observed in the Phase 3 clinical trials. Based on these results, dual therapy with sofosbuvir and RBV is FDA-approved for patients with HCC awaiting LT and available data support aiming for at least 4 weeks of HCV RNA negativity prior to treatment in order to achieve pTVR(10).

PRE-TRANSPLANT ANTIVIRAL THERAPY IN DECOMPENSATED CIRRHOSIS

Pre-transplant treatment to achieve SVR

While a primary goal of antiviral treatment to achieve SVR among wait-listed patients with decompensated cirrhosis is to prevent post-LT HCV recurrence, it is possible that HCV eradication will prevent the need for LT in some patients. Histologic regression of HCV cirrhosis has been demonstrated in a small number of patients with compensated

cirrhosis who achieved SVR with PEG-IFN-based treatment(26, 27). Numerous studies have also shown improved clinical outcomes among patients with compensated cirrhosis who achieve SVR, including an increase in LT-free survival and a decrease in hepatic decompensation, HCC, liver-related mortality, and all-cause mortality(27-32). Although the impact of antiviral therapy on the natural history of *decompensated* HCV cirrhosis is less clear, as this patient population has had limited treatment options, a study of 75 HCV patients with decompensated cirrhosis treated with PEG-IFN and RBV demonstrated significantly lower rates of further decompensation events and hospitalizations(33). However, interferon-based therapy is contraindicated in the setting of decompensated disease due to the increased risk of adverse events including serious infection, worsened liver failure, and death(22, 34).

While it will undoubtedly be tempting to use interferon-free regimens among decompensated cirrhotics, it is important to note that published clinical trials exclude patients with evidence of decompensation. The safety and efficacy of simeprevir has not been studied in patients with Child-Pugh B or C and therefore should be avoided in these patients, as it is unclear how hepatic impairment affects drug metabolism(35). In contrast, safety data for use of sofosbuvir and ribavirin as well as sofosbuvir-ledipasvir in patients with decompensated cirrhosis exists, and treatment appears to be well tolerated despite in patients with advanced disease (36, 37, 39).

SVR data for dual therapy of sofosbuvir and ribavirin in pre-LT patients with decompensated cirrhosis are lacking. Treatment response to ledipasvir-sofosbuvir *without RBV* has been studied among a small number of genotype 1 patients with decompensated cirrhosis and is lower than reported rates in compensated cirrhotics(38). Among 20 patients with Child Pugh B cirrhosis, 13 (65%) achieved SVR12 after 12 weeks of treatment and 7 relapsed. None of the participants discontinued treatment due to adverse events. Ledipasvir-sofosbuvir *with RBV* (escalating doses starting at 600 mg/day) was evaluated in a larger study of 59 patients with Child Pugh B cirrhosis and 49 patients with Child Pugh C cirrhosis(39). Overall, SVR12 was achieved in 45/52 (87%) of patients treated for 12 weeks and 42/47 (89%) of patients treated for 24 weeks (Figure 1). Serious treatment-related adverse events were rare. Treatment was discontinued early due to adverse events in 3 patients, and 6 patients died (4 septic shock, 1 renal failure, 1 cardiac arrest). Six patients

underwent transplant during the study period and were not included in the analysis: one patient died 2 weeks after transplant and 5 continued to have undetected HCV RNA at the time that preliminary results were presented.

Pre-transplant treatment to prevent HCV recurrence

Available data suggest that sofosbuvir and RBV dual therapy is effective at achieving on-treatment virologic response and is well-tolerated in patients with decompensated cirrhosis. Among 25 patients with genotype 1-4 HCV compensated (Child-Pugh A) or decompensated (Child-Pugh B) cirrhosis and portal hypertension who received sofosbuvir and RBV, all except one decompensated patient had an undetectable HCV RNA level by week 8 of treatment (Figure 2) (37). All patients had a hepatic venous pressure gradient (HVPG) >6 mmHg, and most (78%) had a HVPG >12 mmHg. The majority of patients were genotype 1, treatment experienced, and decompensated. Importantly, only one patient discontinued treatment due to an adverse event (periorbital rash). None of the treated patients developed new or worsening decompensation, and improvements in ascites and hepatic encephalopathy were observed. Further experience with sofosbuvir in the setting of decompensated cirrhosis has also been gained in the compassionate use program for patients with severe recurrent HCV after LT, as well be described later in this review. On-treatment virologic response is also high in patients with genotype 1 and 4 decompensated cirrhosis treated with ledipasvir-sofosbuvir and RBV.

Taken together, while data are limited, treatment with sofosbuvir and RBV dual therapy or ledipasvir-sofosbuvir and RBV is generally safe and well tolerated in patients with decompensated cirrhosis. Our practice has been to initiate treatment among patients with relatively predictable waiting list times, typically patients with MELD exception points for HCC or patients with living donors, approximately 3 months before anticipated or planned surgery with the goal of achieving undetectable HCV RNA for at least 4 weeks before LT. The optimal or minimal dose of RBV needed to support achievement of an on-treatment response is unknown and side effects related to RBV, especially in decompensated patients with baseline anemia and/or renal dysfunction, may limit tolerability of the dual therapy regimen. Initiation of

RBV at a dose of 600 mg daily (rather than usual 1000-1200 mg daily) and adjusting based on hemoglobin levels, may be a safer treatment approach in these patients.

SUMMARY OF PRE-TRANSPLANT ANTIVIRAL THERAPY

●Consider antiviral treatment to achieve SVR in patients with well-compensated cirrhosis (such as patients with HCC) and a high likelihood of SVR based on genotype and prior treatment experience.

●In most patients with decompensated cirrhosis, the goals of pre-LT antiviral therapy are to achieve and maintain on-treatment undetectable HCV RNA up to the time of LT in order to achieve pTVR.

●Duration of on-treatment undetectable HCV RNA pre-LT is an important predictor of pTVR.

●Interferon-based treatment should be avoided in pre-LT patients with decompensated cirrhosis due to the risk of serious adverse events and infection.

●Simeprevir has not been studied in patients with decompensated cirrhosis.

●Sofosbuvir and RBV dual therapy and ledipasvir-sofosbuvir with RBV triple therapy appear to be generally safe in patients with decompensated cirrhosis. Treatment aimed at preventing post-LT recurrence should be started approximately 3 months before anticipated surgery with the goal of achieving undetectable HCV RNA for ≥4 weeks pre-LT. Start with low dose of RBV and adjust based on response and anemia.

POST-TRANSPLANT ANTIVIRAL THERAPY IN COMPENSATED CIRRHOSIS

Prior treatment guidelines recommended antiviral therapy in the presence of moderate fibrosis (≥F2 on a scale of 4), moderate or severe necroinflammatory activity (≥A3 on scale of 4), or cholestatic hepatitis(40). Preemptive therapy with PEG-IFN and RBV, started within the first 6 months post-LT and typically prior to the established presence of fibrosis, is no more effective than delaying treatment until disease progression is evident. Achievement of SVR post-LT is associated with improved graft and patient survival(41).

Multiple, mostly single center, studies have investigated the efficacy of PEG-IFN and RBV post-LT (42-44). SVR rates are ~30% for genotype 1 and 60-75% for genotype non-1. Dose reductions are frequently required, and discontinuation is common but acute and chronic rejection are infrequent, occurring in 2% and <1% respectively(42, 43).

Although telaprevir and boceprevir are not approved for treatment of transplant recipients, off-label use occurred due to the desperate need for effective therapies, especially among patients with advanced fibrosis for whom the risk of progression to graft loss is significant. In the CRUSH-C cohort, the largest series to date of post-LT genotype 1 HCV patients who underwent PI-based triple therapy, SVR12 was 61% among 95 patients, suggesting nearly 2-fold higher cure rates are achievable with PI-triple therapy than with PEG-IFN and RBV, although head-to-head comparisons have not been performed(45).

However, as in the pre-LT population, tolerability and safety are significant challenges. Anemia is the most frequently observed side effect of PI-based triple therapy in the post-LT setting. Despite RBV dose reduction and erythropoietin (EPO) use in over 80% of CRUSH-C participants, 59% still required red blood cell transfusion during the first 16 weeks after starting the PI. Interestingly, renal dysfunction was common: over one third of CRUSH-C patients developed a creatinine rise of > 0.5 mg/dL. Pungpapong and colleagues similarly found a creatinine rise > 0.5 mg/dL in 38% of their cohort, with a median rise of 0.4-0.5 mg/dL(46). This may be a result of calcineurin inhibitor toxicity from either altered pharmacokinetics in the setting of CYP3A4/5 inhibition or P-glycoprotein inhibition due to the PI, leading to increased calcineurin inhibitor concentration in the renal tubules(47). Finally, telaprevir and boceprevir are both substrates for and inhibitors of the CYP3A4/5 pathway and affect the metabolism of drugs metabolized by this pathway, including cyclosporine, tacrolimus, and sirolimus. In healthy volunteers, coadministration of boceprevir increased the dose-normalized (DN) area under the curve (AUC) of cyclosporine by 2.7-fold and the DN AUC of tacrolimus by 17-fold(48). Telaprevir increased the DN AUC of cyclosporine by 4.6-fold and the DN AUC of tacrolimus by 70-fold(49). In LT-recipients, telaprevir increased the DN AUC of sirolimus by 26-fold(50). Therefore, post-LT HCV treatment with telaprevir or boceprevir requires immunosuppressant dose adjustments and close monitoring of therapeutic levels. Given these challenges, telaprevir and boceprevir-based triple therapy is not expected to have a role in post-LT HCV therapy, except in those countries without access to newer DAAs.

Although data currently are scarce, it is anticipated that all-oral antiviral regimens will be highly effective and safe in the post-LT setting. A phase 2 clinical trial investigated the efficacy and safety of dual therapy with sofosbuvir and RBV for 24 weeks in post-LT patients with recurrent HCV(51). Forty patients with genotype 1-4 HCV who were at least 6 months post-LT were enrolled. All patients had Child-Pugh ≤7 and MELD ≤17, and patients with signs of decompensation were excluded. RBV was started at 400 mg per day and was escalated based on hemoglobin levels. All patients achieved end-of-treatment response, and 70% achieved SVR12 (Figure 3). Average daily RBV dose was comparable between patients with and without relapse. Anemia requiring EPO and/or blood transfusion occurred in 20% of patients. There were no deaths, graft losses, or episodes of rejection reported. Importantly, there are no significant drug-drug interactions between sofosbuvir and tacrolimus or cyclosporine(52). Given this favorable safety profile, dual therapy with sofosbuvir and ribavirin is recommended by the AASLD-IDSA for post-LT patients with compensated genotype 2 or 3 disease(53). When used post-LT, RBV should be started at 600 mg/day and increased by as tolerated to achieve weight-based dosing.

For genotype 1 patients post-LT, real-world experience with the use of sofosbuvir and simeprevir post-LT is emerging. In the HCV-TARGET consortium, 131 post-LT patients were treated with sofosbuvir and simeprevir with or without RBV, and 61/68 (90%) have achieved SVR4(54). An additional study of 109 post-LT patients treated with this regimen demonstrated SVR12 in 60/66 (91%) patients who had been followed long enough to reach the outcome(55). One patient in the latter study died due to drug-induced liver injury which developed while on treatment. Serious adverse events were rare in both studies, and there were no episodes of graft rejection. Simeprevir does not appear to have clinically significant interactions with tacrolimus(56). However, cyclosporine increases the levels of simeprevir approximately 6-fold and this combination is not recommended(57).

The AASLD-IDSA recommends daily sofosbuvir plus simeprevir, with or without RBV, for 12 to 24 weeks in compensated genotype 1 patients post-LT. These recommendations will likely change with to the recent FDA approval of ledipasvir-sofosbuvir(11). Ledipasvir-sofosbuvir with RBV for 12 or 24 weeks is currently being investigated in a phase 2

study of genotype 1 and 4 post-LT patients with and without cirrhosis, including patients with decompensated disease(58). To date, 223 patients have been treated, including 51 with Child Pugh A, 52 with Child Pugh B, and 9 with Child Pugh C cirrhosis. Among the participants with F0-F3 fibrosis or Child Pugh A cirrhosis, SVR12 was achieved in 78/81 (96%) and 79/81 (98%) with 12 and 24 weeks of treatment, respectively (Figure 3). Fatigue, anemia, headache, and nausea were the most common adverse events, and serious adverse events were rare.

The all-oral combination of ritonavir-boosted paritaprevir, co-formulated with ombitasvir, plus dasabuvir and RBV for 24 weeks has been evaluated in a phase 2 trial of post-LT recipients with genotype 1 HCV(59). Enrolled patients had METAVIR ≤F2 fibrosis and were stable on tacrolimus- or cyclosporine-based immunosuppressant regimens. Among 34 patients enrolled, SVR12 was achieved in 97% (Figure 3). The one relapse occurred 3 days after treatment discontinuation, and the patient had evidence of NS3, NS5A, and NS5B resistant variants which were not present at baseline. Serious adverse events occurred in 2 patients, and 1 patient discontinued the study drugs due to adverse events. RBV was dosed at the discretion of the treating physician; 600-800 mg/day was the most common dose at baseline (56%) and at the end of treatment (68%). One-third of patients experienced anemia; 5 patients received EPO, and none received a blood transfusion. Tacrolimus and cyclosporine dose adjustments were required: the recommended tacrolimus dose was modified to 0.5 mg per week or 0.2 mg every 3 days, and the recommended cyclosporine dose reduction was 20% of pre-treatment daily dose. No episodes of rejection occurred.

Additional regimens under evaluation in post-LT patients without decompensated cirrhosis include simeprevir and sofosbuvir with and without ribavirin for genotype 1 HCV (ClinicalTrials.gov identifier NCT02165189), simeprevir, daclatasvir, and ribavirin for genotype 1b HCV (ClinicalTrials.gov identifier NCT01938625), and daclatasvir, sofosbuvir and ribavirin in genotype 1-6 HCV (ClinicalTrials.gov identifier NCT02032875).

POST-TRANSPLANT ANTIVIRAL THERAPY IN DECOMPENSATED CIRRHOSIS

Post-LT experience with sofosbuvir and RBV, with or without PEG-IFN, in patients with decompensated cirrhosis was attained in a compassionate access program for patients with aggressive post-LT HCV(36). The study population was comprised of patients with genotype 1-4 HCV with severe recurrence post-LT and a less than 1 year life expectancy. Among 104 patients enrolled, 72 completed 24-48 weeks of treatment (7 discontinuations due to adverse events, 12 repeat LT, and 13 deaths). Reflecting the severity of illness in the cohort, the median MELD was 15 and ranged from 6 to 43. Overall, excluding repeat LT and patients without data available, 62% of patients achieved SVR12.

In preliminary results of the phase 2 study of ledipasvir-sofosbuvir with RBV for 12 or 24 weeks post-LT, patients with decompensated cirrhosis tolerated treatment well and had relatively high treatment response (58). SVR12 was 81% in both the 12 and 24 week arms among the patients with Child Pugh B or C cirrhosis (overall 42/52) (Figure 3). Of the 10 patients who did not achieve SVR, 3 relapsed, 5 died, and 1 withdrew consent. None of the deaths were believed to be related to treatment. Only one subject with decompensated cirrhosis had a treatment-related serious adverse event (hemolytic anemia), and 3 patients discontinued treatment due to adverse events.

Another study evaluated the safety and efficacy of sofosbuvir and daclatasvir with or without RBV among 12 post-LT patients with severe recurrent HCV who were treated through an international compassionate use program(60). Three patients had fibrosing cholestatic HCV and 9 had cirrhosis. The mean MELD at baseline was 22 and mean Child-Pugh score was 10. During treatment, 3 deaths occurred: one due to rapidly progressive liver failure, one due to gastrointestinal bleeding, and one due to septic shock. Severe adverse events occurred among 4 of the remaining 9 patients and were attributed to the severity of the patients' underlying liver disease rather than directly to the antiviral treatment. The 9 patients who completed 24 weeks of treatment all had undetectable HCV RNA at the end of treatment. At the time the study was published, post-treatment virologic data was available for 5 patients, all of whom had achieved SVR4. In this series as well as an additional case report describing the successful treatment of a patient with post-LT fibrosing cholestatic HCV with sofosbuvir and daclatasvir for 24 weeks, there were no apparent drug-drug interactions between either DAA and tacrolimus (60, 61).

Finally, high rates of virologic and clinical response were seen in 23 patients with post-LT fibrosing cholestatic HCV treated with sofosbuvir (n=8) or sofosbuvir and daclatasvir (n=15) based regimens(62). Improvement in clinical laboratory parameters was noted in 87% of patients within the first 8 weeks of treatment. SVR12 was achieved in 7/8 (88%) treated with sofosbuvir and RBV with or without PEG-IFN and 11/11 (100%) treated with sofosbuvir and daclatasvir with or without RBV. No treatment-related serious adverse events or significant drug-drug interactions were noted. Safety and efficacy data for use of the other new DAA agents among post-LT patients with decompensated disease are not yet available.

SUMMARY OF POST-TRANSPLANT ANTIVIRAL THERAPY

●Antiviral treatment is recommended in patients with ≥F2 fibrosis, ≥A3 necroinflammatory activity, or cholestatic hepatitis.

●Use of telaprevir or boceprevir-based triple therapy in genotype 1 patients is not recommended due to toxicities and drug-drug interactions.

●Sofosbuvir, ledipasvir, and daclatasvir appear to be safe and effective in post-LT patients and simeprevir is safe in post-LT patients with compensated liver disease. Optimal treatment regimens and durations are unclear but will likely be similar to genotype-specific recommendations in the non-LT setting.

●Cyclosporine use with simeprevir is not recommended. There are with no significant interactions between sofosbuvir, ledipasvir and daclatasvir with immunosuppressant medications.

●Future DAA regimens are promising but will require attention to drug-drug interactions.

SUMMARY

HCV recurrence after LT has been a major clinical challenge. Until recently, attempts to prevent or treat HCV recurrence have been limited by poor tolerability and response to interferon-based antiviral therapy. The availability of highly effective and safe all-oral DAAs will undoubtedly improve our ability to prevent and treat recurrent HCV and may decrease the need for LT among patients with decompensated cirrhosis due to HCV. However, limited data exist regarding the efficacy and safety of the new DAAs in the transplant setting. Issues regarding drug resistance and drug-

drug interactions are likely to emerge as experience grows using DAA's in the LT population. "Real-world" cohorts of antiviral therapy in pre- and post-LT patients will remain critical in defining optimal HCV treatment regimens.

Table 1. Characteristics of new HCV direct-acting antiviral drugs

	NS3/4A Protease Inhibitors	**NS5A Replication Complex Inhibitors**	**Nucleotide NS5B Polymerase Inhibitors**	**Non-Nucleoside NS5B Polymerase Inhibitors**
	Paritaprevir (ABT-450)/r Simeprevir Asunaprevir Grazoprevir (MK-5172)	Ombitasvir (ABT-267) Daclatasvir Ledipasvir GS-5816 Elbasvir (MK-8742)	Sofosbuvir	Dasabuvir (ABT-333) Beclabuvir (BMS-791325)
Potency	High	High	Intermediate to high	Low to intermediate
Genotypic coverage	Multi-genotypic	Multi-genotypic	Pan-genotypic	Limited genotypic
Resistance barrier	Intermediate to high	Low to intermediate	High	Low
Special considerations	CYP3A inhibition: ABT-450/r, Simeprevir (mild) CYP3A induction: Asunaprevir (weak) Indirect hyperbilirubinemia: Simeprevir, Paritaprevir (ABT-450)/r		Renal clearance is the major elimination pathway of sofosbuvir	

Table 2: Interferon-free regimens for patients with compensated HCV genotype 1 cirrhosis

	Phase of Development	SVR Compensated Cirrhosis	Comments
SOF + RBV[†] x 24 weeks (23, 53, 63, 64)	Approved	N/A	●Treatment-naïve patients ●Few cirrhotic patients in published clinical trials
SOF + SIM x 12 weeks(12)	Approved	93% (13/14)	●METAVIR F3-F4 patients ●SVR 86% in treatment-naïve, 100% in prior null responders
SOF + SIM x 24 weeks(12)	Approved	100% (16/16)	●SVR 100% in treatment-naïve, 100% in prior null responders
SOF + LDV x 12 weeks (13, 14)	Approved	97% (32/33)	● Treatment-naïve
SOF + LDV x 24 weeks (13, 14)	Approved	100% (22/22)	● Treatment-experienced
Paritaprevir/r-Ombitasvir, dasabuvir, RBV[†] x 12 weeks(15, 65)	Phase 3	92% (191/208)	●Majority treatment-experienced ●SVR 89% in genotype 1a and 99% in genotype 1b
Paritaprevir/r-Ombitasvir, dasabuvir, RBV[†] x 24 weeks(15)	Phase 3	96% (165/172)	●Majority treatment-experienced ●SVR 94% in genotype 1a and 100% in genotype 1b
DCV + ASV x 24 weeks(66)	Phase 3	83% (172/206)	●All genotype 1b ●SVR 91% in treatment-naïve without thrombocytopenia, 87% in prior non-responders without thrombocytopenia, 79% in interferon ineligible/intolerant
DCV + ASV + Beclabuvir +/- RBV x 12 weeks(68)	Phase 3	93% (188/202)	●SVR 96% in treatment-naïve, 90% in treatment-experienced
SOF + DCV +/- RBV[†] x 12 or 24 weeks(69)	Phase 2	N/A	●No patients with cirrhosis in published clinical trial
Grazoprevir + Elbasvir +/- RBV x 12 or 18 weeks(71)	Phase 2	95% (162/171)	●SVR 94% in treatment-naïve, 96% in treatment-experienced

Abbreviations: SVR, sustained virologic response; SOF, sofosbuvir; RBV, ribavirin; SIM, simeprevir; EOT, end of treatment; LDV, ledipasvir; DCV, daclatasvir; r, ritonavir; ASV, asunaprevir

[†]Weight-based RBV

Table 3: Interferon-free regimens for patients with compensated HCV genotype 2 and 3 cirrhosis

	Phase of Development	SVR Compensated Cirrhosis	Comments
Genotype 2			
SOF + RBV[†] x 12 weeks(9, 72)	Approved	84% (38/45)	●Limited data among cirrhotic treatment-experienced patients suggest improved SVR with 16 weeks versus 12 weeks(9)
SOF + GS-5816 x 12 weeks(73)	Phase 2	N/A	●Treatment naïve ●Preliminary results not available for patients with cirrhosis
SOF + DCV +/- RBV[‡] x 12 or 24 weeks(69)	Phase 2	N/A	●No patients with cirrhosis in published clinical trial ●Genotype 2 and 3 patients
Genotype 3			
SOF + RBV[†] x 24 weeks(72)	Approved	67% (39/58)	● SVR 92% in treatment-naïve, 60% in treatment-experienced
SOF + GS-5816[‡] +/- RBV x 12 weeks(74)	Phase 2	92% (48/52)	●Treatment experienced
SOF + DCV x 12 weeks(75)	Phase 3	63% (20/32)	●SVR 58% in treatment-naïve and 69% in treatment-experienced

Abbreviations: SVR, sustained virologic response; SOF, sofosbuvir; RBV, ribavirin; SIM, simeprevir; LDV, ledipasvir; DCV, daclatasvir

[†]Weight-based RBV

[‡] RBV dosed 800 mg daily

[‡]GS-5816 100 mg daily

FIGURE LEGENDS

Figure 1. SVR12 rates among 99 HCV genotype 1 and 4 patients with decompensated cirrhosis treated with ledipasvir-sofosbuvir and ribavirin for 12 or 24 weeks (39).

Abbreviations: SVR12, sustained virologic response 12 weeks after treatment discontinuation; CTP, Child-Turcotte-Pugh score; SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin; wks, weeks

Figure 2. On-treatment virologic response on sofosbuvir and weight-based RBV among HCV genotype 1-4 with cirrhosis and portal hypertension(37).

Abbreviations: LLOQ, lower limit of quantification; CTP, Child-Turcotte-Pugh score

Figure 3. Post-LT virologic response among 40 genotype 1-4 patients treated with sofosbuvir and RBV for 24 weeks, 34 genotype 1 patients treated with Paritaprevir/r/Ombitasvir, dasabuvir, and RBV for 24 weeks, and 214 genotype 1 and 4 patients treated with ledipasvir-sofosbuvir and RBV for 12 or 24 weeks *in separate non head-to-head studies (51, 58, 59)*. The SOF + RBV trial included 4 patients with CTP score 7. All patients in the Paritaprevir/r/ombitasvir + dasabuvir + RBV trial had Metavir ≤F2 fibrosis.

Abbreviations: SOF, sofosbuvir; RBV, ribavirin; r, ritonavir; LDV, ledipasvir; wks, weeks; EOT, end of treatment; CTP, Child-Turcotte-Pugh score; SVR12, sustained virologic response 12 weeks after treatment discontinuation

REFERENCES

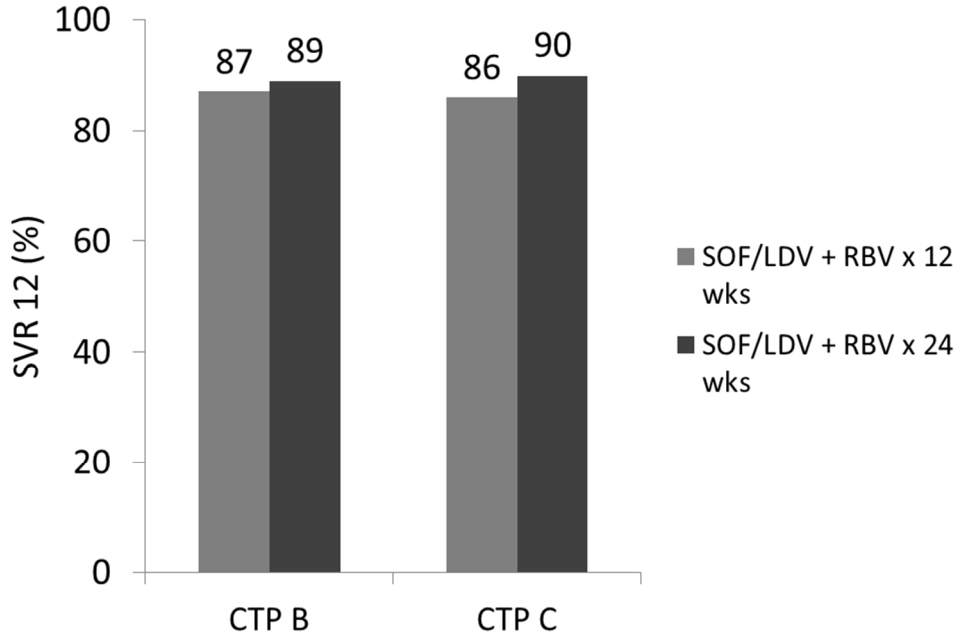
1. WHO. http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index4.html#incidence.
2. Kim WR, Stock PG, Smith JM, Heimbach JK, Skeans MA, Edwards EB, et al. OPTN/SRTR 2011 Annual Data Report: liver. Am J Transplant. 2013;13 Suppl 1:73-102.
3. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology. 2002;122(4):889-96.
4. Berenguer M, Schuppan D. Progression of liver fibrosis in post-transplant hepatitis C: Mechanisms, assessment and treatment. J Hepatol. 2012.
5. Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. Liver Transpl. 2010;16(11):1228-35.
6. Berenguer M, Roche B, Aguilera V, Duclos-Vallee JC, Navarro L, Rubin A, et al. Efficacy of the retreatment of hepatitis C virus infections after liver transplantation: role of an aggressive approach. Liver Transpl. 2013;19(1):69-77.
7. Everson GT, Trotter J, Forman L, Kugelmas M, Halprin A, Fey B, et al. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. Hepatology. 2005;42(2):255-62.
8. Tekin F, Gunsar F, Karasu Z, Akarca U, Ersoz G. Safety, tolerability, and efficacy of pegylated-interferon alfa-2a plus ribavirin in HCV-related decompensated cirrhotics. Aliment Pharmacol Ther. 2008;27(11):1081-5.
9. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013;368(20):1867-77.
10. Sovaldi [package insert]. Gilead Sciences, Inc.,Foster City, CA; 2013.
11. AASLD, IDSA, IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://wwwhcvguidelinesorg.
12. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014.
13. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. N Engl J Med. 2014.
14. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370(16):1483-93.
15. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. N Engl J Med. 2014.
16. Thomas RM, Brems JJ, Guzman-Hartman G, Yong S, Cavaliere P, Van Thiel DH. Infection with chronic hepatitis C virus and liver transplantation: a role for interferon therapy before transplantation. Liver Transpl. 2003;9(9):905-15.
17. Forns X, Garcia-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. J Hepatol. 2003;39(3):389-96.
18. Everson GT, Terrault NA, Lok AS, Rodrigo DR, Brown RS, Jr., Saab S, et al. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. Hepatology. 2012.
19. Carrion JA, Martinez-Bauer E, Crespo G, Ramirez S, Perez-del-Pulgar S, Garcia-Valdecasas JC, et al. Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: A retrospective study. J Hepatol. 2009;50(4):719-28.
20. Massoumi H, Elsiesy H, Khaitova V, Peterson B, Norkus E, Grewal P, et al. An escalating dose regimen of pegylated interferon and ribavirin in HCV cirrhotic patients referred for liver transplant. Transplantation. 2009;88(5):729-35.
21. Hezode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, et al. Effectiveness of Telaprevir or Boceprevir in Treatment-experienced Patients with HCV Genotype 1 Infection and Cirrhosis. Gastroenterology. 2014.

22. Saxena V, Manos MM, Yee HS, Catalli L, Wayne E, Murphy RC, et al. Telaprevir or boceprevir triple therapy in patients with chronic hepatitis C and varying severity of cirrhosis. Aliment Pharmacol Ther. 2014;39(10):1213-24.
23. Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013;310(8):804-11.
24. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368(20):1878-87.
25. Curry MP, Forns X, Chung RT, Terrault NA, Brown R, Jr., Fenkel JM, et al. Sofosbuvir and Ribavirin Prevent Recurrence of HCV Infection after Liver Transplantation: An Open-Label Study. Gastroenterology. 2014.
26. D'Ambrosio R, Aghemo A, Rumi MG, Ronchi G, Donato MF, Paradis V, et al. A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. Hepatology. 2012;56(2):532-43.
27. Mallet V, Gilgenkrantz H, Serpaggi J, Verkarre V, Vallet-Pichard A, Fontaine H, et al. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med. 2008;149(6):399-403.
28. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnu L, Mazzella G, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007;45(3):579-87.
29. Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010;52(5):652-7.
30. Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010;52(3):833-44.
31. Fernandez-Rodriguez CM, Alonso S, Martinez SM, Forns X, Sanchez-Tapias JM, Rincon D, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: outcomes and factors predicting response. Am J Gastroenterol. 2010;105(10):2164-72; quiz 73.
32. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584-93.
33. Iacobellis A, Siciliano M, Perri F, Annicchiarico BE, Leandro G, Caruso N, et al. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study. J Hepatol. 2007;46(2):206-12.
34. Hezode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol. 2013.
35. Olysio [package insert]. Janseen Therapeutics, Titusville NJ; 2013.
36. Forns X, Prieto M, Charlton M, McHutchinson JG, Symonds WT, Brainard D, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C including fibrosing cholestatic hepatitis following liver transplantation. Program and abstracts of the 49th Annual Meeting of the European Association for the Study of the Liver; April 9-13, 2014; London, England. Abstract O62.
37. Afdhal N, Everson G, Calleja J, al. E. Sofosbuvir and ribavirin for the treatment chronic HCV with cirrhosis and portal hypertension with and without decompensation: early virologic response and safety. Program and abstracts of the 49th Annual Meeting of the European Association for the Study of the Liver; April 9-13, 2014; London, England. Abstract O68.
38. Gane E, Hyland R, An D, al. e. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. Program and abstracts of the 49th Annual Meeting of the European Association for the Study of the Liver; April 9-13, 2014; London, England. Abstract 06. .
39. Flamm SF, Everson GT, Charlton M, Denning JM, Arterburn S, Brandt-Sarif T, et al. Ledipasvir/Sofosbuvir with ribavirin for the treatment of HCV in patients with decompensated cirrhosis: preliminary results of a prospective,

multicenter study. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract 239.
40. Wiesner RH, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. Liver Transpl. 2003;9(11):S1-9.
41. Berenguer M, Palau A, Aguilera V, Rayon JM, Juan FS, Prieto M. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant. 2008;8(3):679-87.
42. Wang CS, Ko HH, Yoshida EM, Marra CA, Richardson K. Interferon-based combination anti-viral therapy for hepatitis C virus after liver transplantation: a review and quantitative analysis. Am J Transplant. 2006;6(7):1586-99.
43. Berenguer M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. J Hepatol. 2008;49(2):274-87.
44. Xirouchakis E, Triantos C, Manousou P, Sigalas A, Calvaruso V, Corbani A, et al. Pegylated-interferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis: systematic review and meta-analysis of prospective controlled studies. J Viral Hepat. 2008;15(10):699-709.
45. Burton JR, Jr., O'Leary JG, Verna EC, Saxena V, Dodge JL, Stravitz RT, et al. A US Multicenter Study of Hepatitis C Treatment of Liver Transplant Recipients with Protease-Inhibitor Triple Therapy. J Hepatol. 2014.
46. Pungpapong S, Aqel BA, Koning L, Murphy JL, Henry TM, Ryland KL, et al. Multicenter experience using telaprevir or boceprevir with peginterferon and ribavirin to treat hepatitis C genotype 1 after liver transplantation. Liver Transpl. 2013;19(7):690-700.
47. Burton JR, O'Leary JG, Verna EC, Saxena V, Dodge JL, Stavitz RT, et al. A US multicenter study of hepatitis C treatment of liver transplant recipients with protease-inhibitor triple therapy. *In submission*.
48. Hulskotte E, Gupta S, Xuan F, van Zutven M, O'Mara E, Feng HP, et al. Pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and cyclosporine and tacrolimus in healthy volunteers. Hepatology. 2012;56(5):1622-30.
49. Garg V, van Heeswijk R, Lee JE, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology. 2011;54(1):20-7.
50. O'Leary JG, McKenna GJ, Klintmalm GB, Davis GL. Effect of telaprevir on the pharmacokinetics of sirolimus in liver transplant recipients. Liver Transpl. 2013;19(4):463-5.
51. Charlton M, Gane E, Manns MP, Brown RS, Jr., Curry MP, Kwo PY, et al. Sofosbuvir and Ribavirin for Treatment of Compensated Recurrent Hepatitis C Virus Infection After Liver Transplantation. Gastroenterology. 2014.
52. Castellares C, Barreiro P, Martin-Carbonero L, Labarga P, Vispo ME, Casado R, et al. Liver cirrhosis in HIV-infected patients: prevalence, aetiology and clinical outcome. J Viral Hepat. 2008;15(3):165-72.
53. Sulkowski M, Rodriguez-Torres M, Lalezari JP, al. e. All-Oral Therapy with Sofosbuvir Plus Ribavirin for the treatment of HCV genotype 1,2 and 3 infection in patients coinfected with HIV (PHOTON-1). AASLD Annual Meeting 2013. Nov 1-5, 2013, 2013c; Washington, DC.
54. Brown RS, Reddy K, O'Leary JG, Kuo A, Morelli G, Stratvitz R, et al. Safety and efficacy of new DAA-based therapy for hepatitis C post-transplant: interval results from the HCV-TARGET longitudinal, observational study. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract LB-4.
55. Pungpapong S, Werner KT, Aqel B, Leise MD, Murphy JL, Henry TM, et al. Multicenter experience using sofosbuvir and simeprevir with/without ribavirin to treat HCV genotype 1 after liver transplantation. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract 9.
56. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38(2):518-26.
57. Janssen R&D (Posted 2013). A study of pharmacokinetics, efficacy, safety, tolerability, of the combination of simeprevir (TMC435), daclatasvir (BMS-790052), and ribavirin (RBV) in patients with recurrent chronic hepatitis C genotype 1b infection after orthotopic liver transplantation (NCT01938625). http://www.clinicaltrials.gov/ct2/show/NCT01938625. September 5, 2014.

58. Reddy KR, Everson GT, Flamm SL, Denning JM, Arterburn S, Brandt-Sarif T, et al. Ledipasvir-sofosbuvir with ribavirin for the tretment of HCV in patients with post transplant recurrence: preliminary results of a prospective, multicenter study. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract 8.
59. Mantry P, Kwo P, Coakley E, Te H, Vargas H, Brown Jr. RS, et al. CORAL-I [M12-999]: ABT-450/r/ombitasvir (ABT-267) + dasabuvir (ABT-333) + ribavirin in liver transplant recipients with recurrent HCV genotype 1 infection. Program and abstracts of the World Transplant Congress; July 26-31, 2014; San Francisco, CA. Abstract 1325.
60. Pellicelli AM, Montalbano M, Lionetti R, Durand C, Ferenci P, D'Offizi G, et al. Sofosbuvir plus daclatasvir for post-transplant recurrent hepatitis C: Potent antiviral activity but no clinical benefit if treatment is given late. Dig Liver Dis. 2014.
61. Fontana RJ, Hughes EA, Bifano M, Appelman H, Dimitrova D, Hindes R, et al. Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. Am J Transplant. 2013;13(6):1601-5.
62. Leroy V, Dumortier J, Coilly A, Sebagh M, Fougerou-Leurent C, Radenne S, et al. High rates of virological response and major clinical improvement during sofosbuvir and daclatasvir-based regiments for the treatment of fibrosing cholestatic HCV-recurrence after liver transplantation: The ANRS CO23 CUPILT study. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract 21.
63. Lalezari L, Nelson DR, Hyland RH, al. E. Once daily sofosbuvir plus ribavirin for 12 and 24 weeks in treatment-naive patients with HCV infection: the QUANTUM study. Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver. April 24-28, 2013, 2013.
64. Gane EJ, Stedman CA, Hyland RH, al. e. Once daily sofosbuvir plus ribavirin for 12 and 24 weeks in treatment-naive patients with HCV infection: the QUANTUM study. . Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver. April 24-28, 2013, 2013b; Amsterdam, the Netherlands.
65. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370(17):1594-603.
66. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet. 2014.
67. Everson GT, Sims KD, Rodriguez-Torres M, Hezode C, Lawitz E, Bourliere M, et al. Efficacy of an interferon- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naive patients with HCV genotype 1 infection. Gastroenterology. 2014;146(2):420-9.
68. Muir A, Poordad F, Lalezari JP, Everson GT, Dore GJ, Kwo P, et al. All-oral fixed dose combination therapy with daclatasvir/asunaprevir/BMS-791325, +/- ribavirin, for patients with chronic HCV genotype 1 infection and compensated cirrhosis: UNITY-2 Phase 3 SVR12 results. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract LB-2.
69. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370(3):211-21.
70. Lawitz E, Hezode C, Gane E, Tam E, Lagging M, Balart L, et al. Efficacy and safety of MK-5172 and MK-8742 ± ribavirin in hepatitis C genotype 1 infected patients with cirrhosis or previous null-response: the C-WORTHY study. Program and abstracts of the 49th Annual Meeting of the European Association for the Study of the Liver; April 9-13, 2014; London, England Abstract O61
71. Lawitz E, Gane EJ, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of MK-5172 and MK-8742 +/- ribavirin in hepatitis C genotype 1 infected patients wtih cirrhosis or previous null response: final results of the C-WORTHY study (parts A and B). Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract 196.
72. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. N Engl J Med. 2014.

73. Everson GT, Tran TT, Towner WJ, Davis MN, Wyles D, Nahass R, et al. Saftery and efficacy of treatment with the interferon-free, ribavirin-free combination of sofosbuvir + GS-5816 for 12 weeks in treatment naive patients with genotype 1-6 HCV infection. Program and abstracts of the 49th Annual Meeting of the European Association for the Study of the Liver; April 9-13, 2014; London, England Abstract O111.
74. Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, et al. High efficacy of treatment with sofosbuvir + GS-5816 +/- ribavirin for 12 weeks in treatment experienced patients with genotype 1 or 3 HCV infection. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract 197.
75. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week combination treatment with daclatasvir (DCV) and sofosbuvir (sof) in patients infected with HCV genotype (GT) 3: ALLY-3 phase 3 study. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases; November 7-11, 2014; Boston, Massachusetts Abstract LB-3.



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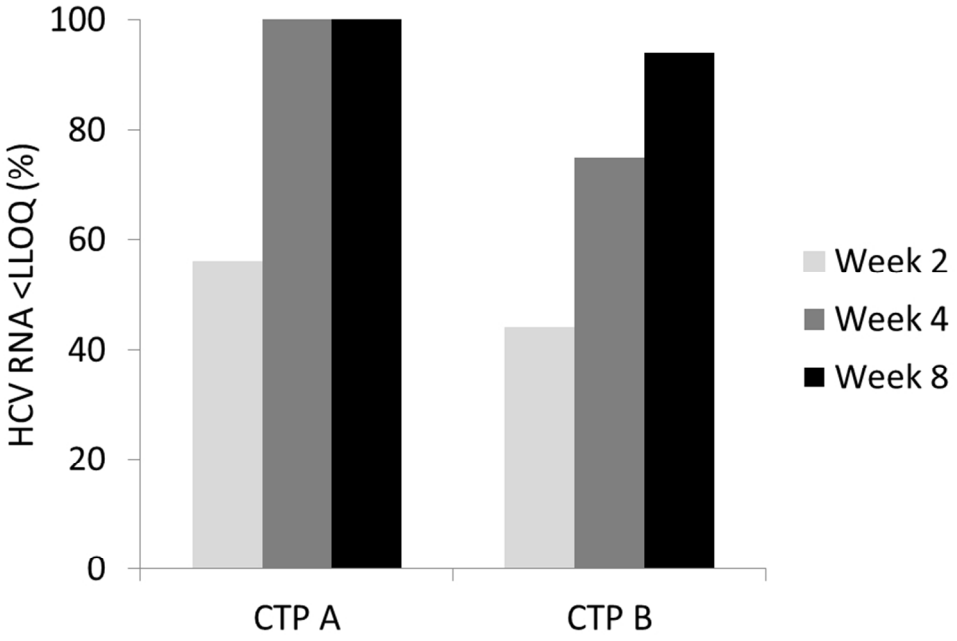

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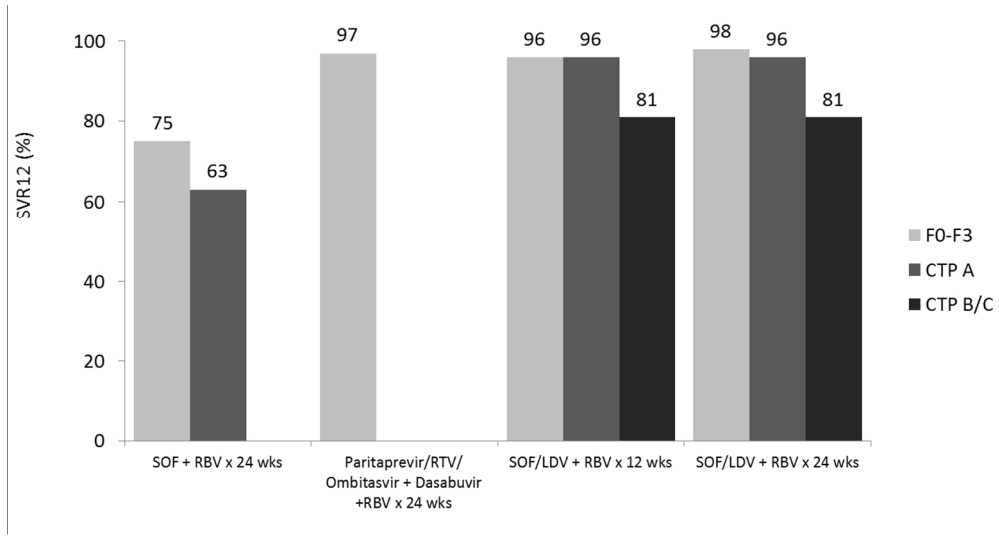

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